UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,445	08/24/2006	Michael E. Jung	58086-235854 (2004-129-2)	6734

26694 7590 03/02/2009

VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
03/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,445	JUNG ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-17* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 9-10 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 9-17 are pending.

Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on November 24th 2008 is acknowledged. Claims 7-8 were cancelled, claims 1,9 and 10 were amended and new claims 15-18 were added.

Claims 3-6 and 11-14 are withdrawn from consideration as being drawn to a non-elected invention.

Claims under consideration are claims 1-2, 9-10 and 15-18

Applicants' arguments, filed 11/24/2008 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Restriction requirement

Applicants arguments against the Restriction requirement in the arguments/remarks filed on 11/24/2008 has been fully considered but not found to be persuasive for the reasons of record restated below.

Examiner would like to reiterate where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or

corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. Each of the three restricted Groups I-III is defined by a different special technical feature as detailed in the office action of 07/23/2009. Accordingly there is no same or corresponding special technical features unifying Groups I-III and thereby they lack unity.

The restriction requirement is therefore proper and made final

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

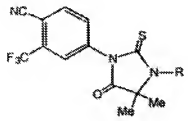
Rejection of 1-2 and 9-10 under 35 U.S.C. 103(a) as being unpatentable over Sovak et al (US 5656651, referenced in the IDS) in view of Chu et al. (US 6949521) **is maintained** for reasons of record restated below.

Newly added claims 15-18 are rejected as being drawn to the same subject matter as previously rejected instant claims 1-2 and 7-8 (claim set of 08/24/2006) under this reference as restated below. Accordingly, claims 15-18 are properly rejected under this same rejection.

New limitation in the amended claim 1 was made to rectify a republication error as discussed in Applicant's paper submitted on July 7th 2008. The amendment does not change the scope of the claim 1 which was originally rejected under this rejection and accordingly remains properly rejected here.

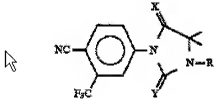
New limitations in the amended instant claims 9 and 10 are the limitations of claims 7-8 from the previous claim set submitted on 08/24/2006 which have been incorporated into the previously rejected claims 9 and 10. Claims 7-8 are currently cancelled, however, since the subject matter of previous claims 7-8 was properly rejected under this rejection in the previous action of (07/23/2008), has been cancelled in the amended claims set filed on 11/24/2008. Accordingly, the currently amended claims 9 and 10 which merely incorporates the subject matter of previously rejected claims 7-8 are also properly rejected under this rejection.

Instant claims 1-2, 9-10 and 15-18 are towards a composition of matter comprising a compound having the formula shown below and a pharmaceutically acceptable carrier.



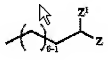
wherein R is $(CH_2)_nN_3$ or $N_3C_6H_4$ and where n is from 3 to 8.

Sovak teaches substituted phenylthiohydantoins for use in detecting the presence of tumor cells having androgenic receptors and providing for cytostatic and cytotoxic activity toward such cells (abstract). Sovak teaches N-substituted arylthio-4', 4'-dimethylhydantoins and that the compound finds uses in diagnosis and/or therapy associated with androgenic receptors and that the subject compounds have high affinity for androgen receptors of a variety of cell types and are able to exert at least one of proliferation inhibition or cytotoxicity for thereby or preferential binding for use as a detecting medium for cells and tissues comprising androgen receptors or for other identification. (col.2, lines 25-36). Sovak teaches that tissue comprising cells with androgen receptors include prostate tissue, ovary tissue testes etc (col.3, lines 4-6). Sovak teaches compounds having the following formula



Wherein X is oxygen or nitrogen, with the proviso that when R is iodoaryl, X may be sulfur; Y is sulphur, with the proviso that when R is iodoaryl group, Y may be

sulphur, oxygen or nitrogen, preferably X and Y are different; R is an organic group, which may be aliphatic, alicyclic, aromatic, heterocyclic, or combinations thereof as defined below. The first group of compounds will comprise monothiohydantoins, where the other oxo group of the hydantoin will be oxygen or nitrogen. These groups will, for the most part, have R having the following formula



Wherein: Z is hydroxyl, amino, a substituted amino or a 4-diazolyl, particularly a 4-(1',3'-imidazolyl); Z^1 is hydrogen, hydroxyl, or may be taken together with Z to provide for olefinic or acetylenic unsaturation, or a 2,2-dimethyldioxalane. (col.3, lines 7-41)

Sovak teaches that the substitutent on amino nitrogen may be varied widely, depending upon the use of the compound. For cytotoxicity or antiproliferative activity, the amino group may be unsubstituted or substituted, particularly with the single acyl group, where the acyl group may serve to enhance the activity of the compound by changing its pharmacokinetic activities, by providing for a second cytotoxic or antiproliferative compound, by providing for a chelating agent for chelating a metal ion, particularly a radioactive metal or non-metallic on, for carrying a radioopaque atom, or the like. Radioactive elements include fluorine, iodine, gadolinium, technetium, etc (col.3, lines 42-53). Sovak further teaches that various cytotoxic agents such as methotrexate, taxol, adriamycin etc. may be employed which are joined to the subject hydantoins by any convenient linking groups which does not significantly diminish the cytotoxic or

antiproliferative activity of the compound (col.4, lines 27-32). Sovak teaches that the subject compositions may be formulated in accordance with conventional ways for use in vivo. The subject compounds are found to be stable in human plasma at physiological temperatures. The subject compounds are found to have substantially greater cytostatic and cytotoxic effects in inhibiting cell growth for neoplastic cells, as compared to normal cells, i.e. having a high therapeutic index. The subject compositions are readily formulated in conventional carriers, such as saline, phosphate buffered saline, vegetable oils, ethanol, or other physiologically acceptable carrier (col.5, lines 7-17). Accordingly Sovak provides one of ordinary skill in the art motivation to develop composition comprising phenylthiohydantoin derivatives.

What Sovak does not teach is the specific compound claimed in instant application wherein the N substitution is either a $(CH_2)_n N_3$ n=3-8 or $C_6H_4 N_3$.

This deficiency is cured by the teachings of Chu et al

Chu et al teaches prodrug compositions comprising azide derivatives of drugs which are capable of being converted to the drug in vivo. (abstract) Among the preferred class of azide derivative Chu teaches those of nucleoside analogs , azide derivatives of aminoglycoside antibiotics which are primary amines, ketones, or hydroxy-substituted compounds, Azide derivatives of sulfonamides which are primary amines or ketones and azide derivatives of biologically active acyclic amines, ketones and hydroxy-substituted compounds, including arylalkyl, heterocyclic arylalky, and cyclic aliphatic compounds where the amine or oxygen moiety is on the ring (col.1, lines 1-65)). Chu additionally teaches that the corresponding azides may be formed for drugs useful for

virtually any therapeutic purposes, so as to increase the half-lives of said drugs and suitable drugs can be identified by those skilled in the art form those having amine, carbonyl or hydroxy substituents. Additionally, Chu teaches that formulation of corresponding azides may be readily accomplished by those of ordinary skill in the art without undue experimentation by means known in the art (col. 12, lines 28-46). Accordingly Chu provides one or ordinary skill in the art motivation to derivatize a known drug with an azide functionality to extend the half-life of that particular drug.

Regarding the properties recited in claims 9-10 wherein the compound inhibits the growth of hormone refractory prostate cancer cells, wherein the compound has been previously subjected to a method of examining the physiological effect etc.), a composition and its properties cannot be separated. The composition and the compound are understood to carry the characteristics associated with them. The prior art does not measure the properties recited in the instant claims 9 and 10, however, because the prior art compositions has the similar components as required by applicant's claims, it necessarily must exhibit and have the same properties. Thus the properties of instant claim 9-10 are inherent to the prior art compositions. Office lacks laboratory facilities to test the prior art compositions. It is incumbent upon applicants to provide data demonstrating that the properties of the disclosed prior art compositions are different from the claimed compositions. Thus, because the prior art compositions are the same as claimed by applicants, the recited properties are inherent to the prior art compositions

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. The primary reference teaches structurally related compounds to those claimed in the instant application which possess cytotoxic effects and the secondary reference of Chu teaches that modification of the amine group in any known therapeutics to azide group increases the bioavailability and half-life of the known therapeutic thereby increasing its efficacy. Accordingly, It would have been *prima facie* obvious to the skilled artisan to combine the teachings of Sovak and Chu to synthesize the instantly claimed compound. An ordinarily skilled artisan would have been motivated to use the dimethylphenylhydantoin, N-substituted with amine moiety taught by Sovak and modify the amine function to azide functionality as taught by Chu to increase the effectiveness of the original compound for treatment of prostate cancer. A skilled artisan will be imbued with a reasonable expectation of success in developing such a dosage form based on the state of the art at the time of invention in order to develop an effective therapeutic agent with prolonged half lives and better bioavailability.

Response to applicant's arguments filed on 11/24/2008:

Applicant traverses the above rejection with the following arguments:

(a) Chu teaches nothing pertinent to Sovak or the compounds of the present claim and the compounds claimed in Chu are further limited to those which have an azide

substituted on the 6-carbon of a purine ring. (b) the metabolism of nucleotides referred to by Chu would not be relevant to the compounds of Sovak and has no bearing on the hydantoin compounds instantly claimed (c) Sovac compounds are not presented as drugs for which prodrugs would be desirable.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this instance, Chu et al reference is included in this rejection for the teachings that prodrug compositions comprising azide derivatives of drugs which are capable of being converted to the drug in vivo. Although Chu does not specifically teach the hydantoin compounds taught by Sovak or the compounds claimed in the instant applications, Cho provides motivation to one of ordinary skill in the art to modify a compound with a primary amine to an azide derivative from his teaching that the preferred class of azide derivative include those of nucleoside analogs, azide derivatives of aminoglycoside antibiotics which are primary amines, ketones, or hydroxy-substituted compounds, Azide derivatives of sulfonamides which are primary amines or ketones and azide derivatives of biologically active acyclic amines, ketones and hydroxy-substituted compounds, including arylalkyl, heterocyclic arylalky, and cyclic aliphatic compounds where the amine or oxygen moiety is on the ring (col.1, lines 1-65).

With regards to Applicant's argument that Chu teaches azide derivatization of 6- amino purines only, examiner finds this argument nonpersuasive. Additionally, Chu teaches that formulation of corresponding azides may be readily accomplished by those of ordinary skill in the art without undue experimentation by means known in the art (col. 12, lines 28-46). In addition to purine compounds derivatized by azide, also teaches derivatives of aminoglycosides or sulfonamides which are primary amine, ketones or hydroxyl substituted compounds, biologically activated amines such as serotonin etc. As such Chu explicitly provides motivation to one of ordinary skill in the art to utilize this method of azide derivatization of a drug to improve bioavailability of that specific drug. In response to applicant's argument against Sovac compounds, Sovac provides thiohydantoin compounds to which he says various cytotoxic agents may be employed which are joined to the subject hydantoin by any convenient linkage group. As such Sovac provides one of ordinary skill in the art to utilize one of the compounds taught by Sovac, such as the one wherein the R in Sovac's formula 1 which is substituted with an alkyl or aryl moiety and derivitize it to include azide as taught by Chu et al.

In response to applicant's argument that there is no suggestion to combine the references, .the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this instant an ordinarily

skilled artisan would have been motivated to use the dimethylphenyl hydantoin, N-substituted with amine moiety taught by Sovak and modify the amine function to azide functionality as taught by Chu to increase the effectiveness of the original compound for treatment of prostate cancer. A skilled artisan will be imbued with a reasonable expectation of success in developing such a dosage form based on the state of the art at the time of invention in order to develop an effective therapeutic agent with prolonged half lives and better bioavailability.

Conclusion

Claims 1-2, 9-10 and 15-18 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614